Original Article

Hemodynamic Influences of Azelnidipine, a Novel Calcium Channel Blocker, on Cerebral Circulation in Hypertensive Patients with Ischemic White Matter Lesions

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Calcium channel blockers have been widely used for the treatment of hypertension because several clinical trials have demonstrated their strong action on lowering blood pressure and their role in preventing cardiovascular events such as stroke and coronary heart disease. However, there have been few reports on the effects on cerebral hemodynamics when blood pressure is lowered with this class of drug. In this study, we used positron emission tomography and acetazolamide challenge tests to measure cerebral blood flow and cerebrovascular reserve before and after administration of a novel calcium channel blocker, azelnidipine, in nine hypertensive patients (mean age, 66.1 years) with ischemic white matter lesions. Systemic blood pressure was significantly decreased from baseline (153.8±15.5/92.1±8.5 mmHg) after treatment with azelnidipine (138.4±16.3/81.8±6.2 mmHg). The baseline global cerebral blood flow values before and after treatment were 40.1±7.2 mL/min/100 g and 39.2±8.2 mL/min/100 g, respectively. The cerebrovascular reserve values before and after treatment were 58.6±21.7% and 56.3±21.3%, respectively. Differences in these parameters were not significant. A regional analysis showed no statistical differences in regional cerebral blood flow or cerebral perfusion reserve throughout the brain before and after treatment. No associations between the decreased blood pressure and the changes in cerebral blood flow or cerebrovascular reserve were found in the whole brain or in the deep white matter with ischemic lesions. In conclusion, we found that the cerebral blood flow and cerebral vascular reserve were preserved after blood pressure lowering with azelnidipine administration in hypertensive patients with ischemic white matter lesions. Azelnidipine, a novel calcium channel blocker, could be a feasible antihypertensive regimen in terms of cerebral circulation in patients with ischemic white matter lesions. (*Hypertens Res* 2008; 31: 2147–2154)

***Key Words*: cerebral blood flow, calcium channel blocker, positron emission tomography, azelnidipine, cerebrovascular reactivity**

Introduction

Antihypertensive treatment is strongly recommended for the prevention of cardiovascular events, especially stroke, in hypertensive individuals (*1*, *2*). Among several classes of antihypertensive drugs, calcium channel blockers have been believed to reduce stroke occurrence on the basis of random-

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ized clinical trials (*3*). Previous studies with positron emission tomography (PET) revealed beneficial effects of angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker on cerebral hemodynamics in hypertensive patients with (*4*) or without (*5*) a history of stroke. In contrast, there have been few reports on the effects of calcium channel blockers on cerebral hemodynamics. Ogasawara *et al*. reported an increase of cerebral blood flow (CBF) after treatment with nivaldipine in five stroke patients, as shown with PET (*6*), and Akopov *et al*. found variable effects of nifedipine and nicardipine on CBF using the ^{133}Xe infusion technique (*7*). The effect of blood pressure reduction with calcium channel blockers on cerebral hemodynamics has not been examined thoroughly.

With recent progress in brain imaging techniques, we can detect the ischemic white matter lesions that are characteristic of patients who are at high risk for stroke and dementia (*8*–*10*). In hypertensive patients with these brain lesions, strict management of vascular risk factors, especially hypertension, is recommended. However, there are still some concerns about cerebral hypoperfusion because the severity of periventricular white matter lesions has been shown to be correlated with the magnitude of autoregulatory dysfunction (*11*).

Azelnidipine, a recently developed long-acting dihydropyridine calcium channel blocker, has been shown to increase the expression of endothelial nitric oxide synthase (eNOS) (*12*) and exert an antioxidant and neuroprotectant effect against ischemic injury (*13*, *14*). However, the effect of azelnidipine on cerebral hemodynamics has not been examined.

The purpose of this study is to determine the effect of a systemic blood pressure lowering treatment with a novel calcium channel blocker, azelnidipine, on cerebral hemodynamics in hypertensive patients with ischemic white matter lesions using PET and acetazolamide challenge tests.

Methods

Patients

Patients with evidence of ischemic white matter lesions on brain MRI, without significant arterial stenosis and with systolic/diastolic blood pressures of 140/90 mmHg or over, were enrolled from among outpatients of the Department of Neurology and Cardiovascular Medicine, Osaka University Hospital. The protocol was approved by the institutional review board and ethics committee of Osaka University Medical School.

We excluded patients who had already taken calcium channel blockers. We also excluded patients who met any of the following conditions: age under 40 years; uncontrolled diabetes (HbA1c $>8\%$); stroke; myocardial infarction; heart failure; renal failure (serum creatinine >2 mg/dL); severe stenosis ($>75\%$) of the carotid artery and/or middle cerebral artery (assessed by ultrasonography and magnetic resonance angiography, which had been carried out for the clinical assessments); atherosclerosis obliterans; any type of dementia; or currently taking tranquilizers, histamine blockers, analgesics, or diuretics.

During the period from April 2003 through December 2005, nine patients were enrolled. They agreed to participate in the study and provided written consent after receiving a detailed explanation of the study.

Magnetic Resonance Imaging

All patients had undergone brain MRI. All MRIs were performed with a 1.5-T Signa Horizon scanner (GE Yokogawa Medical Systems, Ltd., Tokyo, Japan). The imaging protocol consisted of a T_2-weighted spin-echo, T_1-weighted spin-echo and fluid-attenuated inversion-recovery imaging. White matter lesions were scored in the periventricular and deep subcortical regions separately, according to the rating scale of Fazekas *et al*. (*15*). Fazekas' rating scale provides two scores rated on a 0–3 scale according to the following criteria: Periventricular hyperintensity (PVH) = 0 (absence), 1 ("caps" or pencil-thin lining), 2 (smooth "halo"), or 3 (irregular PVH extending into the deep white matter), and deep white matter hyperintensity (DWMH) = 0 (absence), 1 (punctuate foci), 2 (beginning confluence of foci), or 3 (large confluent areas). The degree of white matter lesion was evaluated as a sum of the scales of PVH and DWMH on each side of the corona radiata. Mild and moderate white matter lesions were defined as 0 to 3 and more than 4, respectively, on this scale.

Drug Control

The patients received a daily oral dose of azelnidipine (CALBLOCK™; Daiichi-Sankyo K.K., Tokyo, Japan) titrated to 16 mg after an initial PET scan. Follow-up medical examinations were performed every 2 to 4 weeks, and the drug dosage was adjusted between 8 and 16 mg/d to achieve a target sitting blood pressure range between 120/70 and 140/90 mmHg. When the sitting blood pressure reached the target range and stabilized with the azelnidipine administration, the patient underwent a second PET scan.

PET and Image Analysis

For CBF measurement, we used PET with an ^{15}O-labeled water injection (*16*). We used a high-performance positron emission tomography scanner (SET-2400W; Shimadzu Co., Kyoto, Japan) that uses 63 slices (slice thickness of 3.1 mm) and a spatial resolution of 3.7 mm full width at half maximum. Regional CBF was quantitatively measured using PET, an ^{15}O-labeled water injection, and an autoradiographic method. During each session, the patient was asked to lie in a supine position on the scanner bed in a quiet, dimly lit room. One session consisted of four scans. First, two consecutive scans were performed, 10 min apart, for the baseline condi-

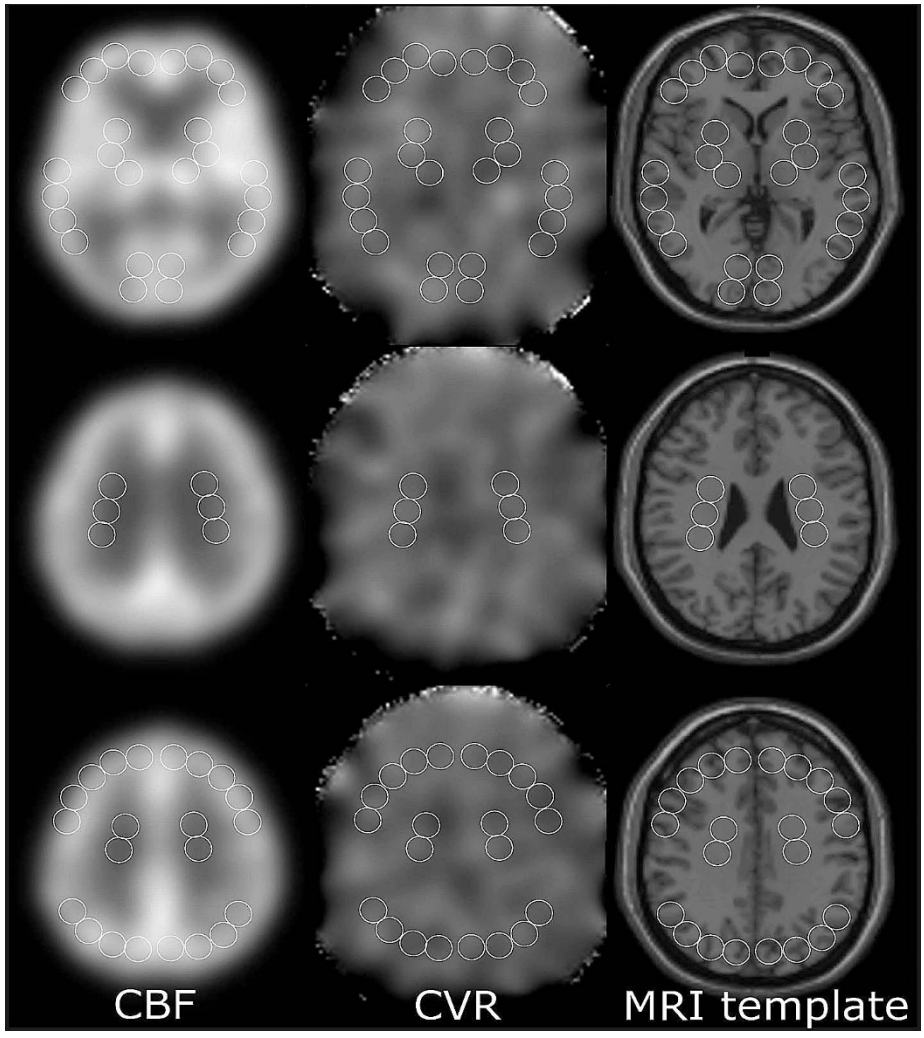

Fig. 1. *Standardized parametric images of cerebral blood flow (CBF) and cerebrovascular reserve (CVR) with regions of interest. The sets of CBF images were realigned and stereotaxically transformed (left column). The CVR images were calculated with the realigned sets of CBF images and also stereotaxically transformed (middle column). The 16-mm circular regions of interest (frontal cortex, temporal cortex, occipital cortex, parietal cortex, basal ganglia areas, thalami, corona radiata, and centrum semiovale) were drawn on standardized CBF images. The standardized MRI T_1 template (right column) was used for drawing the region of interest for the whole cerebrum.*

tion. Then, after intravenous administration of acetazolamide titrated to 1,000 mg, two additional scans were performed in the vasodilated condition. At the end of every scan, the patient's blood pressure, pulse rate, and arterial blood gas tensions were measured. Averaged data of the two measurements were obtained for both the baseline and the vasodilated conditions. Blood pressure was measured using a mercury sphygmomanometer and a 6-inch cuff, with the patient lying supine on the scanner bed.

The regional CBF PET image data sets obtained were realigned and transformed stereotaxically into an identical normal brain template with statistical parametric mapping software (SPM99; Wellcome Department of Cognitive Neurology, University College London, London, UK) running on MATLAB™ 5.3 (The MathWorks Inc., Natic, USA) for Windows™ (Microsoft Inc., Redmond, USA). The regional cerebrovascular reserve (CVR) images were calculated with the realigned sets of CBF images. For CVR, CBF at rest was subtracted from vasodilated CBF, the total was divided by the CBF at rest, and the result was multiplied by 100. The CVR images were transformed stereotaxically with the same parameters of transformation as those of the corresponding CBF images. Identical regions of interest (the whole cerebrum, frontal cortex, temporal cortex, occipital cortex, parietal cortex, basal ganglia areas, thalami, corona radiata, and centrum semiovale) were drawn on the standardized CBF

Table 1. Clinical Characteristics of the Patients

Patients No.	Age	Sex	Dose (mg/d)	Duration (weeks)	Fazekas grade		Coexisting diseases	Medication		
					PVH	DWMH		Antihypertensive	Statin	Antiplatelet
1	58	M	16	30	1	1	HT, HL, DM	none	yes	yes
2	62	F	16	20	1	1	HT, HL	none	none	none
3	65	M	16	31	1	1	HT, HL	none	none	none
4	59	M	8	29	1	1	HT, HL	none	yes	none
5	68	F	16	30	2	2	HT, HL	none	yes	none
6	68	F	8	34	1	2	HT, HL	none	yes	none
7	56	F	8	21	1	1	HT	none	none	none
8	80	M	8	18	1	1	HT	none	none	none
9	68	M	8	19	1	1	HT, HL	ARB	yes	yes

PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity; HT, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; ARB, angiotensin II receptor type 1 blocker.

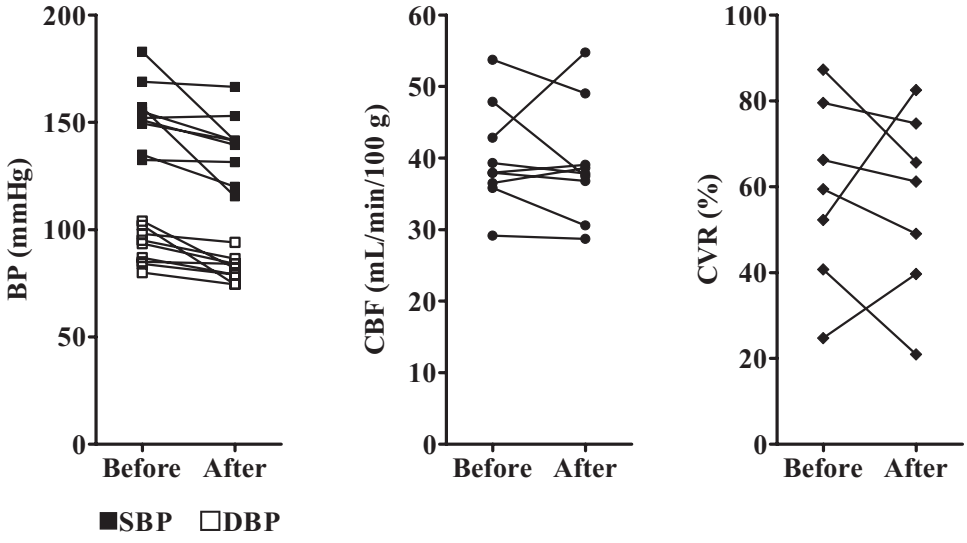

Fig. 2. *Chronic effect of azelnidipine administration on blood pressure (BP), cerebral blood flow (CBF) and cerebrovascular reserve (CVR) in hypertensive patients with brain white matter lesions. Systolic and diastolic blood pressures (SBP and DBP) decreased significantly after azelnidipine administration. In contrast, there were no significant differences in the whole cerebrum CBF and CVR obtained before and after azelnidipine administration.*

images. The region of interest of the whole cerebrum was drawn manually on all slices of the standardized MRI T_1 template provided by SPM and applied for the obtained standardized CBF images. The remaining regions of interest were drawn; each consisted of multiple small circular subregions of interest (16 mm in diameter) linked together (Fig. 1).

Statistical Analysis

Data are presented as means±SD. Blood pressure, pulse rate, arterial blood gas tensions, and baseline CBF values in the cerebrum obtained before and after treatment were compared using paired *t*-tests. The effects of acetazolamide on an increased CBF were analyzed using a one-way analysis of variance (ANOVA). These analyses were performed using statistical analysis software (SPSS 13J for windows; SPSS Japan Inc., Tokyo, Japan). Differences were considered to be significant when the statistical *p* value was less than 0.05.

Results

Baseline characteristics of each patient are given in Table 1. The mean age of the patients was 66.1±6.6 (mean±SD) years. All nine patients showed severity of higher than Fazekas grade 1 in both PVH and DWMH on brain MRI. One patient showed moderate PVH and DWMH. Other patients showed mild PVH on head MRI. Although one patient had already received angiotensin II type 1 receptor blocker

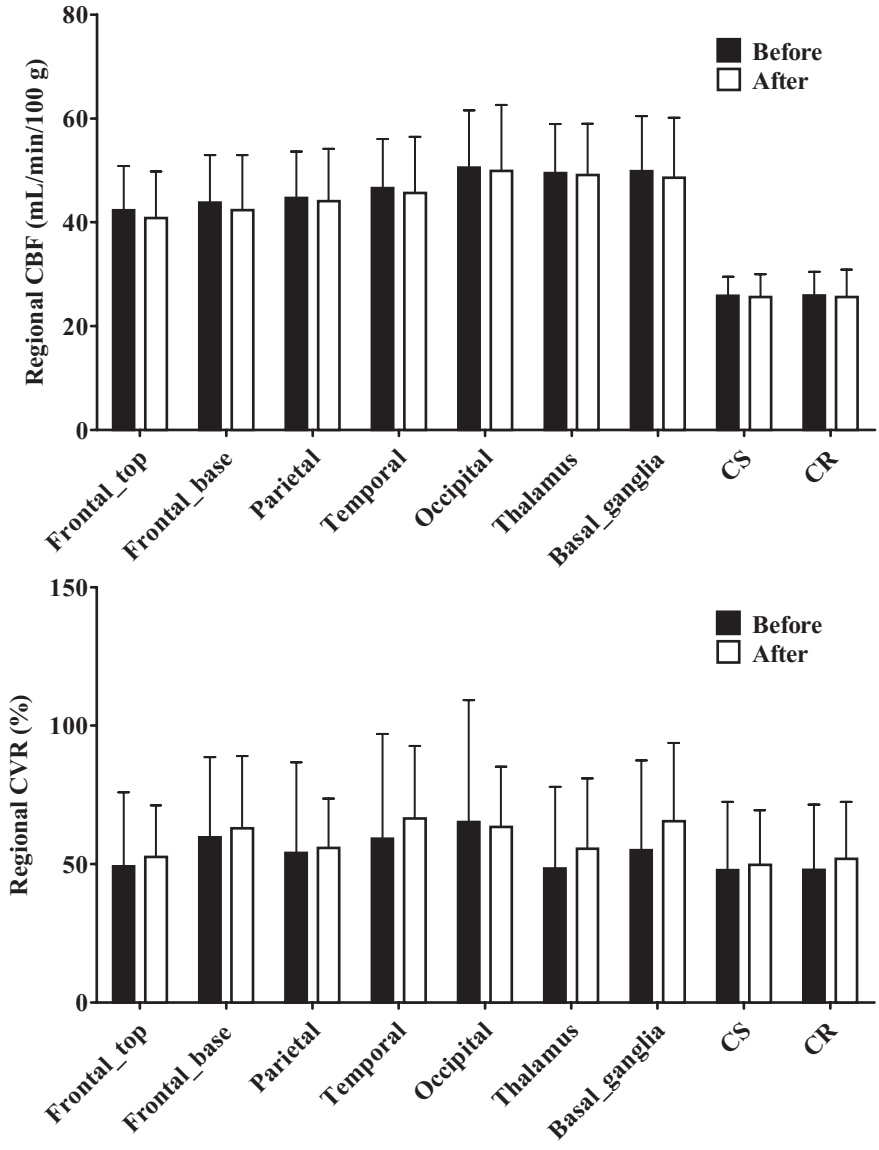

Fig. 3. *Chronic effect of azelnidipine administration on regional cerebral blood flow (CBF) and cerebrovascular reserve (CVR) in hypertensive patients with brain white matter lesions. The CBF in the white matter regions such as the corona radiata (CR) and centrum semiovale (CS) was almost half that in gray matters. Local CVR values in white matter were almost the same as those in gray matter. There were no significant differences in the baseline CBF and CVR obtained before and after azelnidipine treatment, in both the gray and white matter. Values are means±SD for 9 subjects (CBF) or 7 subjects (CVR).*

(ARB), his blood pressure levels were over 140/90 mmHg. Two patients were on antiplatelet therapy. Prescriptions for chronic diseases such as hypercholesterolemia were continued unchanged throughout the study period. Azelnidipine was well tolerated by all the patients, and no complications or adverse effects occurred. The second PET scan was done at 26±6 weeks (ranging from 18 to 34 weeks) after azelnidipine administration. Two patients refused to undergo acetazolamide administration at the second PET scan. The baseline systemic blood pressures before and after azelnidipine administration were 153.8±15.5/92.1±8.5 mmHg and 138.1±16.3/81.8±6.2 mmHg, respectively (Fig. 2). Both the systolic and diastolic blood pressures decreased significantly after azelnidipine administration. The other physiological variables determined both before and after azelnidipine treatment were $PaCO_2$ (before, 39.6±2.7 mmHg: after, 38.3±2.5 mmHg), PaO_2 (before, 74.6±12.0 mmHg: after, 72.7±11.7 mmHg), pH (before, 7.41±0.01: after, 7.42±0.02) and pulse rate (before, 68.4±8.5 bpm: after, 71.2±13.2 bpm). There were no significant differences in these parameters between the measurements before and after azelnidipine treatment. The baseline global CBF values before and after treatment were

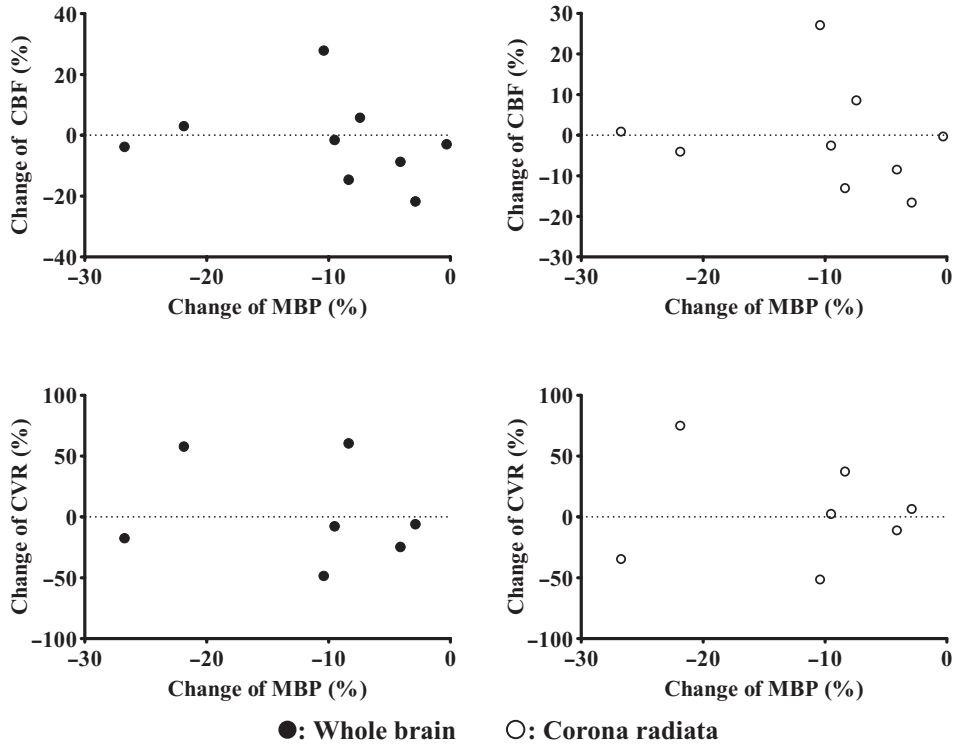

Fig. 4. *Relation between the change in cerebral blood flow (CBF) or cerebrovascular reserve (CVR) and the change in mean blood pressure (MBP). The percent change in MBP and the percent change in CBF or CVR of the whole brain and corona radiata were plotted for each patient. The degree of blood pressure reduction was not correlated with the change in CBF or CVR after azelnidipine therapy, in both the whole brain and the corona radiata.*

40.1±7.2 mL/min/100 g and 39.2±8.2 mL/min/100 g, respectively (Fig. 2). Whole CBF was increased in 4 patients and decreased in 5 patients. The CVR values before and after treatment were 58.6±21.7% and 56.3±21.3%, respectively (Fig. 2). Five patients showed a decrease in CVR, and 2 patients showed an increase in CVR. The differences in these parameters were not significant.

The same relationships were seen for every brain region. Local CBF values were 26.0±4.5 and 25.9±3.6 mL/min/100 g in white matter such as the corona radiata and centrum semiovale, respectively, which are almost half of those values found in gray matter (Fig. 3). Local CVR values in white matter were almost the same as those in gray matter. There were no significant differences in the baseline CBF and CVR obtained before and after azelnidipine in either the gray or the white matters. The relation between the percent change in mean blood pressure and the percent change in CBF or CVR of the whole brain and corona radiata in each patient is shown in Fig. 4. The degree of blood pressure reduction was not correlated with the change of CBF or CVR after azelnidipine therapy.

Discussion

Hypertension is the number one risk factor for stroke and has been recognized as a risk factor for Alzheimer's disease, too (*17*). The reduction of blood pressure markedly prevented stroke occurrence and recurrence in hypertensive patients (*1*, *2*). However, many physicians are still reluctant to lower blood pressure aggressively, especially in elderly patients. Brain MRI studies reported the frequent appearance of ischemic white matter lesions in elderly hypertensive patients (*18*). Autoregulatory dysfunction seen in hypertensive patients with severe periventricular white matter lesions (*11*) lead us to speculate that the aggressive reduction of blood pressure may result in cerebral hypoperfusion in such patients. In this study, we clearly demonstrated that blood pressure reduction with azelnidipine, a novel calcium channel blocker, did not impair CBF and CVR in hypertensive patients with ischemic white matter lesions.

Among calcium channel blockers, azelnidipine has several beneficial effects in terms of cerebral circulation, although the effects of azelnidipine therapy in reducing the rates of stroke and dementia have not yet been published in randomized clinical trials. Lukic-Panin *et al*. demonstrated that azelnidipine treatment showed a greater reduction of infarct volume and cerebral edema than amlodipine treatment in a rat model of middle cerebral artery occlusion (*13*). Iwai *et al*. showed that azelnidipine synergistically enhanced the inhibi-

tory action of ARB on brain ischemia and infarct size in a mouse middle cerebral artery (MCA) occlusion model (*14*). Kimura *et al*. reported that azelnidipine treatment increased eNOS in the brain, suggesting an improvement of brain endothelial function after azelnidipine therapy (*12*).

In animal experiments with mice, rats and cats, calcium channel blockers consistently induced vasodilation in cerebral arteries (*19*, *20*), reduced the thickness of tunica media in cerebral arteries (*21*), increased regional CBF (*22*), preserved microvascular integrity (*23*), and, in spontaneously hypertensive rats, normalized the autoregulatory threshold (*24*). In a randomized clinical trial, amlodipine treatment was shown to reduce the progression of carotid intima-media thickness evaluated with ultrasonography (*25*). However, there are surprisingly few data on the effect of calcium channel blockers on CBF. Only one study, by Ogasawara *et al*., employed PET for quantitative measurement of CBF (*6*). They reported an increase of CBF after treatment with nivaldipine, seen with PET, although there were only five subjects. Using a ^{133}Xe infusion technique, Akopov *et al*. also reported an increase of CBF in hypertensive patients after isradipine treatment, although they showed that treatment with isradipine reduced cerebral perfusion in almost half of the patients with internal carotid artery stenosis (*7*). Several other studies reported an increase of CBF in hypertensive patients after treatment with calcium channel blockers, as seen with transcranial Doppler (*26–28*).

In clinical practice, blood pressure reduction with calcium channel blockers is not recommended in acute ischemic stroke because treatment with nimodipine does not improve functional outcome but does increase the early case-fatality rate in acute stroke patients (*29*). However, in randomized clinical trials of hypertensive patients, calcium channel blockers showed an effect on stroke prevention that was almost equal to that of angiotensin-converting enzyme inhibitors or ARBs (*30–32*). This study supported the preventive effect on stroke of calcium channel blockers with respect to cerebral circulation and suggested that calcium channel blockers were preferable in hypertensive patients with ischemic white matter lesions. The effects of calcium channel blockers on cerebral circulation need to be further investigated in hypertensive patients with severe white matter lesions because all nine patients in this study showed only mild to moderate white matter lesions.

In summary, azelnidipine therapy can be a feasible antihypertensive regimen in terms of cerebral circulation in patients with cerebral small vessel disease.

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